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(54) AMELIORANT FOR PRURITUS CUTANEOUS ACCOMPANYING RENAL FAILURE

(57) A pharmaceutical agent for improvement in pruritus cutaneus associated with renal failure and/or for the treatment of renal failure and/or its complications containing as an effective ingredient oligosaccharide or oligosaccharides such as, but not limited to fructo-oligosaccharide, galacto-oligosaccharide, isomalto-oligosaccharide, malto-oligosaccharide, lacto-sucrose and/or xylo-oligosaccharide, in particular, lactulose, rhamnose and lactitol.

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Description

TECHNICAL FIELD

This invention relates to a new pharmaceutical composition for alleviation of various syndromes, in particular pruritus cutaneus, characteristic to renal failure and hemodialysis patients.

BACKGROUND ART

Among the countries all over the world, the hemodialysis therapy is most widely practiced in Japan. This therapy over an extended time, however, induces various serious problems. The hemodialysis therapy for a long time, for example, causes the onset of complications such as cardiovascular disorder, anemia, abnormal bone metabolism, dysbolism, and/or immunodeficiency. In addition, it is said that 60 - 80% of the hemodialysis patients suffer from pruritus cutaneus. Although pruritus cutaneus itself does not impose direct threatening on the life of the patients, its persistent and chronic torment, night and day, is unbearable to the patients, both physically and mentally. From the view point of the maintenance and improvement in the quality of life, pruritus cutaneus is now a big problem in the treatment of the patients.

As a possible cause of pruritus cutaneus, 1. stimulation of the nerve ending by a certain substance accumulated in the blood by renal failure, 2. a decline in the pruritus threshold value due to change in the pH value, etc., or 3. abnormal secretion by the skin glands such as sebaceous glands and sweat glands, is suspected but it is not yet clear what is responsible for it. For its treatment, antihistaminic agent is generally administered but it has limitation in its efficacy. Besides, due to its side effects like drowsiness, vertigo or generalized malaise, its administration must be discontinued in many cases. In addition, anti-allergic agent, adrenocortical agent or tranquilizer is administered but no agent alone can relieve the patients from the torment and establishment of an effective therapy has been expected.

DISCLOSURE OF INVENTION

The applicants of this invention have been conducting their research focusing on alleviation of pruritus cutaneus, among other complications, developed in renal failure patients treated with the hemodialysis therapy for a long time.

As a result, the applicants of this invention have found that oligosaccharide is effective on the treatment of complications, especially pruritus cutaneus, set in the renal failure and renal hemodialysis patients and have completed this invention. This invention provides a pharmaceutical agent that comprises as effective ingredient one, two or more kinds of oligosaccharide for the treatment of the renal failure patients and renal failure patients with complications.

BEST MODE FOR CARRYING OUT THE INVENTION

Details of the invention are described below.

In addition to lactulose which has long been known as a growth factor of bifidobacteria, there have been found various kinds oligosaccharide that show the same effect. It is known that oligosaccharide such as, but not limited to, fructooligosaccharide, galactooligosaccharide, lacto-sucrose, maltooligosaccharide and xylooligosaccharide grow remarkably bifidobacteria in stool and reduce significantly toxic substances like ammonia, amine phenol and cresol in it. There has, however, been no report made so far on the effect of such oligosaccharide on the treatment of renal failure, in particular, on alleviation of pruritus. It is well known that ammonia is produced by deamination of part of protein or amino acids in the intestine by the intestinal bacteria and decomposition of lactulose by bifidobacteria or other intestinal bacteria in the large intestine help promote the production of organic acids like lactic acid, acetic acid, etc. which in turn decrease the pH value and inhibit absorption of ammonia. On account of this effect, lactulose has been used for the treatment of hyperammonemia. It is also known that administration of lactulose suppresses production of amines like phenol, skatole and indole in the intestine and promotes absorption of calcium in the small intestine. Nonetheless, the effect of lactulose on renal failure or its complications, especially pruritus cutaneus, has not been recognized. Renal hypofunction elicits uremic syndrome like insomnia, cephalea, vomiturition, renal anemia, hypertension and edema and they are treated with hemodialysis when they are not improved by the conservative treatment. As substances called uremic toxins that accumulate in the uremic patients and exacerbate the disease such as β2-microglobulin, guanidine compounds, glycated proteins, indole compounds and phenol compounds have been reported, but association of their blood concentration with pruritus cutaneus has not been elucidated. Those toxins, except glycated proteins, can be removed by the hemodialysis therapy but their removal can not necessarily mitigate pruritus cutaneus.

As the frequency of complications that develop in the patients treated with the hemodialysis treatment over a long period of time, cardiovascular complications are 50 - 60% and highest and cardiac failure is the highest cause of death. As complications that seriously affect the daily life of the renal failure patients, there are renal osteodystrophia, dialysis

amyloidosis, anemia and pruritus cutaneus. A pharmaceutical agent under this invention is, among other complications associated with renal failure, most effective on alleviation of pruritus cutaneus. The patients treated with the hemodialysis therapy are held under various diet restrictions and are restricted to ingest salt, water, protein and potassium. Due to restriction of diet, many of the hemodialysis patients suffer from constipation or have difficulty in excretion.

The oligosaccharides in this invention activate intestinal peristalsis by promoting production of organic acids and improve excretion by softening stool. Furthermore, the oligosaccharides under this invention increase intestinal hydration by enhancing the intestinal osmotic pressure, thus enable smooth excretion. The oligosaccharide or oligosaccharides for a pharmaceutical agent under this invention for the treatment of pruritus cutaneus associated with renal failure and/or renal failure and its complications are a general term of oligosaccharide or oligosaccharides having 2 to about 10 monosaccharides glycosidically bonded and, according to the number of monosaccharides bonded, are classified as disaccharide, trisaccharide, tetrasaccharide, etc. In this invention, one, two or more kinds of oligosaccharides such as, but not limited to, fructooligosaccharide, galactooligosaccharide, isomaltooligosaccharide, malto-oligosaccharide, lactosucrose and/or xylooligosaccharide used to achieve the purpose of this invention. Desirable oligosaccharides are disaccharides like, but not limited to, lactulose, trehalose, rhamnose and lactitol. Among those oligosaccharides, lactulose, in particular, is desirable.

Specifically, there is no limitation in the method of administration of the pharmaceutical agent under this invention for the treatment of renal failure, mitigation of pruritus cutaneus and/or improvement in laxation, but oral administration is desirable. Those saccharide or saccharides are supplied in crystal, amorphous powder, or syrup and can be administered to the patients in any form of pharmaceutical preparation like, but not limited to, granule, tablet, powder and syrup In such a pharmaceutical preparation, filler, extender, disintegrator, hemuctant, bonding agent and/or lubricant normally used can be added as required.

A daily dose of the pharmaceutical agent in this invention is, as an anhydride, in the range of 1 gram to 60 grams depending upon age, sex, body weight and symptom of the patients and normally 1 gram to 30 grams are preferred.

Example of pharmaceutical preparation

Lactulose	50 mg
Starch	116 mg
Glyceric fatty acid ester	30 mg
Cellulose	2 mg
Silicon oxide	2 mg
Total	200 mg

Detailed examples of this invention are described hereunder but they in no way limit the scope of this invention.

Example 1

A daily dose of 3 mg was administered orally to the healthy subjects aged 18 to 23 (male 5 and female 3) for 2 weeks and their stool was chronologically collected for the determination of ammonia, phenol, cresol, indole and skatole. Table 1 shows the results.

Table 1 Effect of lactulose on concentration of toxic substances in stool

(μg/1 g of stool)

	Day 0	Day 7	Day 14	Day 7 after end of administration
Ammonia	457	357	346	443
Phenol	18	5	4	17
Cresol	41	24	21	41
Indole	38	11	2	36
Skatole	16	4	2	13

Administration of lactulose decreased significantly the concentration of toxic low molecule nitrides such as ammonia. 7 days after the end of the administration, the concentration of those substances, however, returned to the level prior to the administration.

Example 2

Male Sprangue-Dawley rats (180 g) were administered orally with 500 mg/kg of crystallized lactulose for three days, then their ureter on both sides were ligated for 24 hrs for collection of blood from their heart to test for blood urea nitrogen (BUN) and creatinine in sera. The rats were then terminated. The results of the test are shown in Table 2.

Table 2

Effect of lactulose on acute renal failure rats			
	Number of rats	Creatinine	BUN
Acute renal failure rats (Control group)	6	4.9 ± 0.08	86.9 ± 0.9
Acute renal failure rats (Group administered with lactulose)	6	4.2 ± 0.17 -14%**	75.1 ± 1.1 -14%**
Healthy rats (Control group)	6	0.7 ± 0.02 -86%**	18.5 ± 1.5 -78%**

Mean ± Standard Error **p<0.01

The serum creatinine and BUN in the acute renal failure control group elevated as high as 7.6 times and 4.7 times of those of the healthy control group, respectively, but both serum creatinine and BUN of the acute renal failure group administered with lactulose were lower than those of the renal failure control group by 14%.

Example 3

16 renal hemodialysis patients complaining of constipation were divided into 2 groups. After dinner, 16 mg of lactosucrose to one group and 16 mg of lactulose to the other were orally administered for 4 weeks to examine their effect on laxation and the condition of stool. The results are shown in Table 3.

Table 3

Effect of lactulose and lacto-sucrose on laxation (Average frequency of laxation/Week)		
	Before administration	After Administration
Lactulose	2.1	5.7
Lacto-sucrose	2.4	4.2

Improvement in laxation by both lactulose and lactosucrose was statistically significant. By administration of both, the condition of stool changed from solid hard to banana-like shape and its color also changed from dark brown to yellow allowing easier excretion.

Example 4

After breakfast and dinner, a total of 16 - 24 g of lactulose was administered orally to the 33 renal hemodialysis patients complaining of pruritus cutaneus for 8 weeks. According to the criteria for the severity of pruritus cutaneus in 5 scores (extremely itchy, very itchy, itchy, slightly itchy, no symptom), the effect of administration of lactulose on pruritus cutaneus was determined and evaluated in 5 grades (remarkably effective, effective, slightly effective, unchanged and aggravated) by comparing the scores at the start of and after the administration. The effect of lactulose on pruritus cutaneus and its change with time are shown in Tables 4 and 5, respectively.

Table 4

Effect of lactulose on pruritus cutaneus		
	Number	(%)
Remarkably effective (pruritus cutaneus score improved by at least 3 grades)	1	3.0
Effective (pruritus cutaneus score improved by not more than 2 grades) Slightly effective (pruritus	3	36.4
cutaneus score improved by not more than 1 grade)	4	39.4
Unchanged (pruritus cutaneus score unchanged)	2	21.2
Aggravated (pruritus cutaneus score aggravated)	0	0

Administration of lactitol alleviated itching in 79% of the pruritus cutaneus patients.

Table 5

Change with time in effect of lactulose on pruritus cutaneus		
	Severe pruritus cutaneus patients (extremely itchy + very itchy)	Light pruritus cutaneus patients (slightly itchy + no symptom)
Before administration	54.6%	9.0%
2 weeks after administration	27.3	27.3
4 weeks after administration	12.0	48.6
8 weeks after administration	13.6	50.0

The percentage of the severe pruritus cutaneus patients decreased from 54.6% prior to the administration down to 12% and that of the light pruritus cutaneus patients increased from 9.0% to 50% 4 weeks after the start of administration of lactulose.

INDUSTRIAL APPLICABILITY

Oligosaccharides like, but not limited to, fructooligo-saccharide, galacto-oligosaccharide, isomalto-oligosaccharide, malto-oligosaccharide, lacto-sucrose and xylo-oligosaccharide, in particular, disaccharides such as, but not limited to, lactulose, trehalose, rhamnose and lactitol are effective on the treatment of renal failure or its complications associated with renal hemodialysis patients, especially, pruritus cutaneus.

Claims

1. An agent for improving pruritus cutaneus associated with renal failure, which comprises one, two or more kind or kinds of oligosaccharide or oligosaccharides as an effective ingredient.

2. An agent as claimed in claim 1 wherein said oligosaccharide or oligosaccharides is or are selected from the group consisting of, fructo-oligosaccharide, galacto-oligosaccharide, isomalto-oligosaccharide, malto-oligosaccharide, lacto-sucrose and xylo-oligosaccharide.

3. An agent as claimed in claim 1 wherein said oligosaccharide or oligosaccharides is or are disaccharides.

4. An agent as claimed in claim 3 wherein said disaccharide or disaccharides is or are selected from the group consisting of lactulose, trehalose, rhamnose and lactitol.

5. An agent as claimed in claim 3 wherein disaccharide is lactulose.

6. An agent for the treatment of renal failure and/or its complications, which comprises one, two or more kind or kinds of oligosaccharide or oligosaccharides as an effective ingredient.

7. An agent as claimed in claim 6 wherein said oligosaccharide or oligosaccharides is or are selected from the group consisting of fructo-oligosaccharide, galacto-oligosaccharide, isomalto-oligosaccharide, malto-oligosaccharide, lacto-sucrose, and xylo-oligosaccharide.

8. An agent claimed in claim 6 wherein said saccharide or saccharides is or are a disaccharide or disaccharides.

9. An agent claimed in claim 8 wherein said disaccharide or disaccharides is or are selected from the group consisting of lactulose, trehalose, rhamnose and lactitol.

10. An agent claimed in claim 8 wherein said disaccharide is lactulose.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP96/01576

A. CLASSIFICATION OF SUBJECT MATTER
Int. Cl^6 A61K31/70, C07H3/06
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
Int. Cl^6 A61K31/70, C07H3/06

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JP, 4-190764, A (RNA Kenkyusho Yugen Kaisha), July 9, 1992 (09. 07. 92), Claim; page 2, lower right column (Family: none)	1 - 10
X	Yoshikazu Matsuda et al. "Effects of Lactulose on a Model of Rabbit Acute Renal Failure", Medicine and Pharmacy Vol. 27, No. 1, (1992), P. 49-54	1 - 10

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
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